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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/503,089	02/11/00	PATEL	A 1030-R-00

022469 HM12/0927
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EXAMINER	
CANELLA, K	
ART UNIT	PAPER NUMBER
1642	10

DATE MAILED: 09/27/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.	Applicant(s)
09/503,089	Patel et al
Examiner	**Art Unit**
Karen Canella	1642

-- The MAILING DATE of this communication app ars on the cov r sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3 months* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☐ Responsive to communication(s) filed on _____

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1-25* is/are pending in the applica

4a) Of the above, claim(s) *1-12* is/are withdrawn from considera

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *13-25* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirem

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *5*

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

DETAILED ACTION

1. Please note that the examiner assigned to this application has been changed.

2. Acknowledgment is made of applicants election, with traverse , of Group V. After review and reconsideration, Groups VI-XIV will be rejoined to the elected Group V.

3. Claims 1-25 are pending. Claims 1-12, drawn to non-elected inventions, are withdrawn from consideration. Claims 13-25 are examined on the merits.

Priority

4. Applicant's claim to an earlier filing date based on applications 09/144,914 filed 9/1/98 and 08/749,816, filed 11/15/96 is acknowledged. However, the earliest application upon which priority is claimed fails to provide adequate support under 35 U.S.C. 112 for all the pending claims of this application as neither of the proteins of SEQ ID NO:2 and 4 have been disclosed in either of the aforementioned applications. However, SEQ ID NO:5 was disclosed in the '914 application. As TREK-1 (SEQ ID NO:2 and 4), and TASK (SEQ ID NO:5) both function as mammalian background outward-going K+ rectifiers, and as TASK (SEQ ID NO:5) was disclosed in the '914 application but not in the '816 application, the instant application will be given the priority date of 9/1/98.

Claim Objections

5. Claims 19, 20, 23, 17, 21, 24 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 19, 20, 23, 17, 21, 24 encompass a multitude of polypeptides as they are drawn to amino acid sequences which are 95% identical to TREK-1 or TASK, or the numerous chimeric proteins which can be potentially derived from TREK-1 or TASK.

Claim Rejections - 35 USC § 112

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 25 recites an improper Markush group in that some members of the group represent a defined cell type derived from a particular species, such as COS cell from African Green Monkey, human HeLa cells, Spodoptera cells, Xenopus oocytes and chinese hamster ovary cells, whereas embryonic kidney cells and fibroblasts encompass many species..

8. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 13-25 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for identifying substances having anesthetic properties, wherein said substances produces a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting said substance with TREK, or TASK, does not reasonably provide enablement for a method for identifying substances having anesthetic properties, wherein said substances produce a safe, reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting said substance with variants or chimeras of TREK, or TASK. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The specification teaches human TREK-1 (SEQ ID NO:2), mouse TREK-1 (SEQ ID NO:4) and murine TASK (SEQ ID NO:5) as novel mammalian outward K+ rectifiers, which are potassium channels activated in the presence

of anesthesia, and thus a protein target for the screening of compounds which can act as general anesthetics in mammals. However, it is well known in the art that general anesthetics can produce more that general anesthesia due to binding at a multitude of biologically active sites available within a mammal (Franks and Lieb, Science, 1991, Vol. 254, pp. 427-430, especially page 428, last sentence to page 429, first column, lines 1-3). Therefore, the determination of safety with regard to an anesthesia cannot be made on the basis of a single in vitro assay. Further, claims 19, 20 and 23 are drawn to variants of SEQ ID NO:2, 4 and 5 having 95% identity to SEQ ID NO:2, 4 and 5. However, the specification has not taught how to modify the claimed variants of TREK and TASK in order to preserve the functional properties of the disclosed TREK and TASK. It is well known in the alt that Protein chemistry is probably one of the most unpredictable areas of biotechnology. For example, as disclosed by Burgess et al. (Journal of Cell Biology, 1990, Vol. 111, pp. 2129-2138) replacement of a single lysine reside at position 118 of acidic fibroblast growth factor by glutamic acid led to the substantial loss of heparin binding, receptor binding and biological activity of the protein.. In experiments with transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biological activity of the mitogen.(Lazar et al, Molecular and Cellular Biology, 1988, Vol. 8, pp.1247-1252). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification will often dramatically affect the biological activity and characteristic of a protein. In addition, Fink et al (EMBO, 1996, Vol. 15, pp. 6854-6862) teach that although potassium channel proteins TWIK-1 and TREK-1 have structural similarity with respect to pore-forming domains and transmembrane domains, this does not translate to functional similarity as TWIK-1 is inwardly rectifying and TREK-1 is outwardly rectifying. Clearly, it could not be predicted that a variant of SEQ ID NO:2, 4 or 5 would will function as in a method of screening for compounds which would induce general anesthesia. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and it cannot be predicted from the disclosure how to make/use variants having 95% sequence identity to SEQ ID NO:2, 4 or 5. Further claims 17 and 21 are drawn to chimeric proteins comprising a

portion of murine and human TREK-1 and claim 25 is drawn to c chimeric molecule comprising a portion of TASK and portions of human and murine TREK-1, and for the reasons stated in this paragraph, one of skill in the art would not know how to make and use the resulting chimeric protein. Cao et al (Journal of biological Chemistry, 1995, Vol. 270, pp. 17697-17701) teaches that a hybrid constructs of K+ channels resulted in proteins which were no longer selective for K+ , thus further teaching against the notion that one could anticipate the properties of a chimeric K+ channel. In view of the above, one of skill in the art would be forced into undue experimentation to practice the claimed invention.

Claim Rejections - 35 USC § 103

10. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

11. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103© and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

12. Claims 13, 15, 16, 18, and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franks and Lieb (Nature, 1994, Vol. 367, pp. 607-614) in view of Fink (EMBO, 1996, Vol. 15, pp. 6854-6862). Claim 13 is draw to a method for identifying substances having anesthetic properties, wherein said substances produce a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting a substance with a

mammalian potassium transport protein , wherein said protein exhibits outward-going potassium rectification, and determining the potassium transport activity induced by said substance, wherein an activation of outward-going potassium transport by said substance is indicative of the substance having anesthetic properties. Claims 15 and 16 specify that the potassium transport protein is TREK-1 and SEQ ID NO:1 and 2 respectively. Claim 18 is drawn to the same method objective as claim 13, comprising contacting said substance with COS cells, wherein said COS cells are transfected with a nucleic acid molecule encoding TREK, and express said TREK on the cell surface, wherein the determination of the outward-going potassium transport by TREK-1 is indicative of the substance having anesthetic properties. Claim 20 further specifies that TREK-1, of claim 18, comprises an amino acid sequence that is at least 95% identical to SEQ ID NO:2. Franks and Lieb teach an outward-going K+ channel current in molluscan neurons. Franks and Lieb teach that anesthetics rapidly activate the current, the current is stable over time, and removal of the neuron from the anesthetic halts this current. Franks and Lieb further teach that this K+ channel would be an attractive candidate for a target in general anesthesia as it is present only in neurons which are sensitive to anesthesia. Franks and Lieb do not teach a homologous outward-going K+ channel in mammalian neurons. Fink et al (EMBO, 1996, Vol. 15, pp. 6854-6862) teach the murine TREK-1 protein as an outward-going K+ rectifier channel consisting of SEQ ID NO:4. It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the TREK-1 protein or COS cells recombinantly expressing the TREK-1 protein on the cell surface, in a method of identifying substances having anesthetic properties, comprising contacting a substance with a TREK-1 as the mammalian potassium transport protein. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Franks and Lieb on the utility of an outwardly-rectifying K+channel of mammalian origin as a molecular target for general anesthetics, and the teachings of Fink et al, identifying the TREK-1 protein as the outwardly-rectifying K+channel of mammalian origin, and COS cells comprising the recombinant TREK-1 protein on the cell surface.

13. Claims 13, 14, 22 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Franks and Lieb (Nature, 1994, Vol. 367, pp. 607-614) in view of Duprat et al (EMBO, 1997, Vol. 16, pp. 5464-5471). Claim 13 is draw to a method for identifying substances having anesthetic properties, wherein said substances produce a reversible state of unconsciousness with concurrent amnesia and analgesia in a mammal upon inhalation comprising contacting a substance with a mammalian potassium transport protein , wherein said protein exhibits outward-going potassium rectification, and determining the potassium transport activity induced by said substance, wherein an activation of outward-going potassium transport by said substance is indicative of the substance having anesthetic properties. Claim 14 specifies that the potassium transport protein is TASK. Claim 22 is drawn to the same method objective as claim 13, comprising contacting said substance with transfected cells recombinantly expressing TASK on the cell surface, and determining the potassium transport activity of TASK, wherein an activation of potassium transport is indicative of said substance having anesthetic properties. Claim 25 further specifies that the transfected cells are selected from the group consisting of COS cells, HeLa cells, Spodoptera cells, Xenopus oocytes, embryonic kidney cells, chinese hamster ovary cells, and fibroblasts. Franks and Lieb teach an outward-going K+ channel current in molluscan neurons. Franks and Lieb teach that anesthetics rapidly activate the current, the current is stable over time, and removal of the neuron from the anesthetic halts this current. Franks and Lieb further teach that this K+ channel would be an attractive candidate for a target in general anesthesia as it is present only in neurons which are sensitive to anesthesia. Franks and Lieb do not teach a homologous outward-going K+ channel in mammalian neurons. Duprat et al teach the murine TASK protein as an outward-going K+ rectifier channel consisting of SEQ ID NO:5. Duprat et al teach the recombinant expression of TASK by transfected COS cells and the expression of TASK by Xenopus oocytes microinjected with RNA encoding TASK.
It would have been *prima facia* obvious to one of ordinary skill in the art at the time the claimed invention was made to use the TASK protein, COS cells recombinantly expressing the TASK protein on the cell surface, or xenopus oocytes expressing the TASK protein in a method of identifying substances having anesthetic properties, comprising contacting a substance with a

TASK as the mammalian potassium transport protein. One of ordinary skill in the art would have been motivated to do so with a reasonable expectation of success by the teachings of Franks and Lieb on the utility of an outwardly-rectifying K+channel of mammalian origin as a molecular target for general anesthetics, and the teachings of Duprat et al, identifying the TASK protein as the outwardly-rectifying K+channel of mammalian origin, COS cells comprising the recombinant TASK protein on the cell surface and Xenpous oocytes expressing the TASK protein.

Conclusion

14. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen Canella whose telephone number is (703) 308-8362. The examiner can normally be reached on Monday through Friday from 8:30 am to 6:00 pm. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, can be reached on (703) 308-3995. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Karen A. Canella, Ph.D.

Patent Examiner, Group 1642

September 21, 2001

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